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**MEDICAL NEWS LETTER**

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### Research on Cancer Viruses

There is no doubt that virology now holds great promise in research efforts on the cause and prevention of cancer. Virology has but recently attained this high status. Only in the past few years has the accumulated evidence of a half century of investigation proved sufficient to convince the more skeptical scientists that viruses cause cancer in animals.

In 1903, the French bacteriologist, Borrell, was the first to make the suggestion that cancer might be a viral disease. His countryman, the eminent virologist, Charles Oberling, later pointed out that Borrell reached this conclusion when he failed to find the "microbe of cancer." For years his idea was defensible "mainly because no other offered a satisfactory interpretation."

Over the ensuing years, one researcher after another has made discoveries and demonstrations that have established today's consolidated position. Many years passed before the studies conducted by the early pioneers of virus-cancer research were generally considered to be anything but isolated curiosities. Other paths of cancer research appeared vastly more promising than virology. In the last decade, however, a number of investigators have become interested in virus-cancer research, and have produced an impressive amount of information about animal tumor viruses and the fundamental nature of viruses and cell components.

Dr. Joseph Beard, the eminent virologist at Duke University, has pointed out that studies have "firmly established the principle of virus etiology of well-known examples of mammalian leukemia." He adds, "There now exists a considerable body of information which is not only compatible with the hypothesis of human leukemia, but which provides a substantial and reasonable background for pursuing investigations in man."

Dr. Leon Dmochowski, who with the electron microscope photographed virus-like particles in a variety of mouse and chicken tumor tissues, has conducted some interesting studies on human leukemia. He reported seeing virus-like particles in a biopsy from an enlarged cervical lymph node of a patient with acute lymphatic leukemia. He also reported that cells in the lymph nodes had undergone a number of changes similar to cell changes in affected organs of mouse leukemia and chicken lymphomatosis. The latter is known to be caused by a virus.

One of the latest milestones in virus-cancer research has been the development at the National Cancer Institute of an extract from leukemic tissue of mice produced by the Moloney virus that is so virulent that leukemia has been caused within 10 weeks in 100% of the mice injected on the first day of life. The leukemia agent is a virus and the electron microscope has revealed particles that may be the virus. Unlike other mouse leukemia viruses, the Moloney virus causes the disease in several different strains. Also, it is active against adult as well as newborn animals. None of the mice inoculated with the virus has developed any form of cancer except leukemia.

Along with numerous reports of new virus-caused animal tumors, there have been many discoveries—often seemingly unrelated—in research on virus and cell constituents, their modes of behavior, and other characteristics. Recently, it has become evident that all of these results are very likely pieces of the same large and intricate puzzle. This realization has been greatly responsible for the acceleration and vitality of virus-cancer research today.

Establishing the role of viruses in human cancer might seem a simple matter of finding virus in malignant tissue and then demonstrating that it caused the disease. However, there is a fundamental difficulty: at the present time, there is no way to demonstrate the carcinogenic effect of viruses on human beings. Laboratory techniques must be developed that will attack the problem indirectly.

A key tool in development of such techniques will probably be tissue culture. The number of laboratories where human cells are being grown in tissue culture has greatly increased in recent years. Research of this nature is making wider use of techniques, such as treatment with x-ray or cortisone, that permit human tissue to grow in experimental animals.

Other fundamental studies are providing knowledge of the relationship between the host animal and the virus. One experimenter has shown that there is a quantitative relationship between the amount of virus inoculated and certain biologic properties of the tumor, such as size, length of time before the tumor develops, and length of time before it kills the animal.

One of the principal questions that must be answered is: How do viruses enter a cell and make it cancerous? For many scientists, studies on nucleic acids offer the most promise in this area. In cells, the nucleic acid DNA is localized in the chromosomes which carry the genetic information of cells and determine their form and function. Cells also contain another form of nucleic acid, RNA, most of which is in the cytoplasm.

Viruses are known to consist largely of nucleic acid, either RNA or DNA, and protein. But until fairly recently it was not known whether nucleic acid alone could be responsible for virus activity. Then, almost simultaneously, two investigators found that the RNA of the tobacco mosaic virus showed infectious activity.

In January 1960, scientists reported that DNA had been isolated from the polyoma virus. Cancer was produced in laboratory animals by inoculating them with tissue culture fluids in which the isolated viral DNA was carried. This strongly indicates that DNA can enter a living cell and change the DNA of the cell to make it cancerous.

Such work has exciting implications and acts as a powerful stimulus to scientific imagination. Studies on bacteria and bacterial viruses have shown that genetic material—and thereby heredity traits—can be transferred by a virus from cell to cell by a process known as transduction. This transfer might cause an abnormal malignant change in the cell. Or a viral nucleic acid

might shed its protein coat and enter a cell, become incorporated in the genetic structure of the cell, and modify it so that the cell begins to reproduce abnormally. Bacterial studies also support the concept that latent viral nucleic acid in a cell might be activated by chemical or physical agents and thus initiate malignant growth.

These possibilities and many others constitute a broad challenge to the scientific community as a whole. Intense, collaborative efforts in many disciplines—genetics, cellular biology, chemistry, immunology, to cite just a few—are needed.

If viruses do cause cancer in man, and if these viruses are isolated, what then? How will we apply our knowledge to help save lives?

Prevention is the end result of all cancer research. There has been some success in developing vaccines against virus-caused cancer in animals. On the other hand, attempts to detect antibodies against the Moloney virus have been unsuccessful and have, therefore, hindered work on the development of a vaccine from this virus. This illustrates an important point—the isolation and identification of a cancer-producing virus may not lead to the speedy development of a vaccine.

If human cancer is a virus disease, another approach might be the use of drugs designed to destroy the virus either before it induces cancer or very early in the course of the disease. Laboratory studies of a virus that infects bacteria have shown that selective action by such drugs is possible. The virus studied induces the formation of a particular enzyme necessary for the reproduction of the virus within the cell. A powerful anticancer agent—5-fluorouracil deoxyriboside—will seek out the enzyme which is only in the bacteria infected by virus, combine with it, and thus block the reproduction process.

Some intriguing studies of cancer treatment in human beings have shown that infection of cancer cells with certain viruses destroys some of the cells. The effect is temporary because the patient soon develops antibodies against the virus. In further studies, attempts are being made to inhibit the host's production of antibodies against these viruses, to develop methods of reaching the cancer with sufficiently powerful doses before antibodies develop, and to produce tumor-destroying properties in other human viruses.

Virus-cancer research has come a long way in the past 50 years. The efforts of dedicated scientists in countries all over the world assure us that knowledge of this complex field will steadily increase. It is difficult to imagine what new findings may be just beyond today's horizon. (J. R. Heller, Research on Cancer Viruses: Public Health Rep, 75: 501-506, June 1960)

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It is the province of knowledge to speak and the privilege of wisdom to listen.

—Oliver Wendell Holmes

### Antibiotics in Medicine

Fifteen years ago, the only antibiotic available for systemic use was penicillin. The clinician now has to make a choice from about 15 antibiotics for the generality of bacterial infections apart from others having more restricted indications. A few of these, such as penicillin, were discovered by independent workers; the majority were unearthed—in a literal sense because worldwide soil surveys have been the means of their discovery—by the enterprise of the pharmaceutical industry. During the same period, those engaged in synthetic chemistry have not been idle; several drugs active against tuberculosis have become available, and more names have been added to the already bewildering list of sulfonamides.

The numerous antibiotics now known are not all distinct in their activity; a few are unique in themselves, but the majority fall into groups displaying close similarity of action. The "spectrum" of penicillin with high activity against gram-positive organisms is imitated by the erythromycin group (which includes spiramycin, oleandomycin, and possibly streptogramin and staphylomycin,) and by bacitracin, novobiocin, vancomycin, and ristocetin. Near equality of activity against gram-positive and gram-negative organisms generally is characteristic of the tetracyclines, but their scope embraces rickettsias, the large viruses, and to some extent, the tubercle bacillus. Chloramphenicol, although in some properties unique, has close affinities with this group. Another somewhat heterogeneous group is characterized by high activity against the tubercle bacillus and against gram-negative organisms with lesser activity against gram-positive organisms—particularly streptococci. Foremost in this is streptomycin with which viomycin may be classed solely for its action in tuberculosis. The remainder form the neomycin group—including kanamycin, framycetin, and paromomycin—the usefulness of which is limited by toxicity. An activity directed exclusively against gram-negative organisms is the peculiar property of polymixin. Finally, there are the polyene antibiotics—nystatin, amphotericin, and trichomycin—the only activity of which is against fungi.

Parallel with the discovery of new antibiotics, there have been two other developments militating against their successful use. One has been the appearance of untoward effects from their administration; this includes manifestations of direct toxicity, sensitization phenomena, and the production of superinfections by resistant bacteria which are sometimes more intractable or even more dangerous than the primary disease. The second development—even more threatening to the future usefulness of some of the antibiotics—is the widespread acquisition of bacterial resistance to them.

The part played by the pure scientist as distinct from the clinician in this constantly widening field is not to be forgotten. Although bacteriology, pharmacology, and chemistry are all concerned, it is the chemist alone who can go to the root of the matter by first ascertaining the structure of an antibiotic and then endeavoring to determine why this chemical configuration

confers the power to arrest bacterial growth. If he has not yet fully succeeded in such efforts, a substantial body of knowledge is accumulating on which the rationalization of antibiotic therapy may ultimately be based.

There are aspects of the subject of antibiotics in medicine on which it is not yet possible to dogmatize. They include, naturally, those deeper questions involving interaction between the antibiotic and the individual cell of which knowledge is still imperfect. They also include matters of a much more mundane and practical nature, prominent among which is the value of combinations of antibiotics in relation to single ones. The actual necessity for combined treatment is established in tuberculosis and in enterococcal endocarditis: how far does this principle apply in other infections? Is the use of combinations of antibiotics to be condemned as "shotgun" therapy or commended as discouraging bacterial resistance and, sometimes, as exerting a superior therapeutic effect? Another everyday question about which there is much difference of opinion is the extent to which antibiotics can justifiably be used to prevent possible infection, especially in connection with surgery.

In these and other matters, the aim of any discussion of antibiotics is to provide the reader with well-ascertained information on which he can base his own opinion. Much of it he will not find except in original papers: no development in medicine has ever been at once so rapid and so complex, and would-be authors of books about it may well have been daunted by the fact that anything which takes a long time both to write and to print is likely to be out of date even before publication. (L. P. Garrod, Introduction to a Seminar - Antibiotics in Medicine: Brit Med Bull, 16: 1-2, 1 January 1960)

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### Management in Cirrhosis and Hepatitis

Despite availability of newer procedures for study of hepatic disease, therapeutic measures designed to affect the function of individual hepatic cells have not been forthcoming. Eventual return of function of hepatic tissue in acute processes is dependent upon removal of the injurious agent and the general support of the patient until some degree of stability is restored. While this is also true of more chronic stages of liver injury, development of physiologic and clinical abnormalities in the cirrhotic can be related to the degree of function of the regenerating nodules—whether small or large—which substitute for dying parenchymal liver tissue in the midst of fibrous replacement, cellular exudate, and biliary hyperplasia. It is of interest that an organ which is involved in the numerous functions ascribed to it may carry on certain processes satisfactorily, but be partially or totally deficient with respect to others.

Etiologic Concepts. Because of the enormous reparative power of hepatic tissue, permanent damage may take place over variably long periods

of time only after repeated subclinical insults in insidious cases or after moderate to overwhelming injury in more obvious instances. Some question still exists as to whether alcohol has a specific effect in production of hepatic injury. From experiments, it has been suggested that a caloric factor or specific food requirement is related to hepatic injury associated with alcohol in the presence of dietary deficiencies.

Studies have related choline metabolism to experimental fatty cirrhosis. However, these studies were with animals and the results may not be related to man. Autoimmune phenomena developing against liver cell protein altered by injury has been suggested as a possible perpetuating phenomenon after removal of all injurious factors.

Experimental liver injury may also be produced by diets deficient in sulfur containing amino acids (cystine) and vitamin E. Dispute exists as to whether viral hepatitis in man is a frequent factor in development of the necrogenic effect that is seen in this deficiency. Other dietary deficiencies have been implicated in a cirrhotic-type picture.

The ever increasing number of drugs which produce hepatic injury is not thought to be a major factor in development of cirrhosis; the vast majority of drugs usually result in disease which is transient and often cholestatic in nature.

The relationship of various disease states—Wilson's disease, infectious mononucleosis, diabetes, ulcerative colitis, and regional ileitis—to development of hepatitis is recognized in certain instances, although the mechanism has not been demonstrated.

**Acute Liver Disease.** Because subacute hepatic necrosis may occur insidiously, the opportunity to treat patients may not present itself until some phase of hepatic decompensation occurs. The efficacy of bed rest is not only a clinically observed fact, but also a sound physiologic adjuvant to healing. In acute hepatitis, however, studies have shown that once the serum bilirubin falls below a level of 2 to 3 mg/100 ml, strict bed rest will not hasten recovery. Bilirubin levels and BSP retention should be followed at weekly intervals using improvement in these tests as a guide to increasing activity.

A high protein diet is most efficacious unless ammonia intoxication is present—3000 calories with 150 to 190 gm of protein. No limitation of fat is required and choline supplements are not needed. Multivitamin therapy has been recommended, although it is probably nonspecific. During the early stages of acute hepatitis, when anorexia, nausea, and vomiting may interfere with dietotherapy, intravenous infusion of 5% dextrose in water is recommended.

In the alcoholic, specific nutritional deficiencies are not uncommon, and include multiple or single deficiencies in the vitamin B group and in vitamin C.

Some observers have called attention to the acute hepatic steatosis occurring in alcoholics associated with parenchymal cell necrosis, polymorphonuclear infiltration, Mallory bodies (hyaline, degenerative lesions), and

a severe, often fatal, active hepatocellular disease. Relationship with other forms of malnutrition is not clear and some observers dispute as to whether the hyaline degeneration is a specific lesion. One group considers that more severe disease can be correlated with more frequent hyaline degeneration.

Noninflammatory hyperplasia of the parotid gland has been noted not only in alcoholic cirrhosis, but also in starvation states. Improvement is often seen with concomitant improvement in the liver disease. Specific dietary problems will be found in individual patients. The severe cirrhotic suffering from prolonged anorexia or vomiting may require tube feedings of milk and dextro-maltose because intravenous fluids over prolonged periods do not supply the needed protein and caloric requirements. In the presence of protein toxicity, the latter may have to be specifically limited. In patients with fluid retention with or without ascites, limitation of sodium to 200 to 500 mg per day may be required. In instances where steatorrhea is present, supplementary pancreatic enzymes have been suggested.

Presence of jaundice is not generally a problem unless some form of cholestasis of bile occurs. In these instances, pruritus may be disturbing and often not responsive to antihistamines, mild sedation, intravenous procaine, and ergotamine, although use of starch baths may be temporarily effective. Methyl testosterone orally must be used advisedly because it is an occasional cause of intrahepatic cholestasis.

Anemias are not an uncommon accompaniment of hepatic disease. Macrocytic or occasionally megaloblastic anemias may respond to daily doses of 250 to 1500 micrograms of folic acid. Normocytic anemias may be due to hemodilution, diminution of formation, or increased destruction of red blood cells. Neutropenia and thrombocytopenia may be present and can be treated by supportive measures including transfusions and steroids. Consideration for splenectomy depends upon the severity of the disorder and the feasibility of surgery. Vitamin K therapy may be useful when hypoprothrombinemia is present. Iron therapy and transfusion may be additional agents. Care should be exercised to prevent overzealous use of blood in those instances where blood loss is not the cause of anemia or where the hemoglobin is above 10 to 11 gm.

Prevention of acute hepatitis in individuals exposed to active disease has been noted following prophylactic administration of gamma globulin—0.06 ml per pound of body weight.

Adrenal Steroid Therapy. In the average case of hepatitis, it is agreed that steroid hormones offer no advantages. Its use has been recommended in patients only when the serum bilirubin is greater than 15 mg/100 ml, when anorexia, nausea, or vomiting cannot be controlled, or when hepatic necrosis is marked as evidenced by shrinking liver, coma, fetor, or disturbed sensorium. In these instances, 20 mg ACTH intravenously administered slowly over 8 to 12 hours for 5 days with subsequent reduction in dose as bilirubin falls may be employed. Or prednisone in doses starting with 75 mg daily may be preferred because of lesser effects of sodium retention.

As yet, no general recommendations have been made to cirrhotics with regard to selection for long term therapy with steroids. A trial of the drug may be considered if progression of disease or poor response has occurred after an adequate period of observation on rest and nutritious diet.

Portal Hypertension and Bleeding Varices. Newer techniques for study have pointed out the great variations which may occur from one patient to another. The chief problem of detecting nonbleeding varices and diagnosing their rupture in the case of acute gastrointestinal hemorrhage remains paramount in management of cirrhosis. Various techniques have been utilized in diagnosing the presence of portal hypertension when barium swallow has been negative for varices. Use of esophagoscopy is often valuable; presence of elevated blood ammonia and increased BSP retention may be of additional diagnostic aid.

The possibility that peptic acid erosion may be a factor has led to the suggestion that ulcer-type management may be effective in preventing bleeding, but available data have not always indicated high levels of gastric acid and uropepsin secretions in these patients.

Decompression of the portal vein by portacaval anastomosis appears to be the favored procedure. Dispute exists, however, as to whether the acute bleeding episode which does not respond to medical management should be subjected to immediate ligation of the varices or whether an emergency shunting operation should be performed. Studies of the natural history of bleeding varices with regard to statistical outcome without surgery have raised the question as to the value of shunting procedures. It remains, at present, that in carefully selected cases with adequate liver function, shunting operations may prolong life and decrease morbidity. Institution of prophylactic shunt surgery prior to bleeding is not usually recommended.

Definitive management of the acute bleeding episode is concerned with blood replacement, prevention and treatment of shock, control of bleeding, and measures to minimize or prevent ammonia toxicity and coma.

Ascites. Studies have shown that cases of cirrhosis with ascites appear to develop obstructive changes in the vascular outflow tracts of the liver with resultant outpouring of hepatic lymph from all surfaces of the liver. Hyperaldosteronism has been a frequent finding in these cases, but by itself does not explain the variable development of fluid retention in cirrhosis.

Management of patients with fluid retention begins with restriction of dietary sodium, but with attention to maintenance of adequate nutrients. Use of diuretics is efficacious and the thiazide derivatives have been helpful in this respect. Doses of chlorothiazide vary from 0.5 to 2.0 gm per day. Frequent paracenteses are not advisable; use of salt-poor serum albumin is costly and of brief effectiveness. Antialdosterone drugs have produced inconsistent and variable results and undesirable neurologic disturbances. Administration of spiro lactones or prednisone has been reported to effect diuresis in refractory cases when combined with mercurials.

Hepatic Coma and Ammonia Intoxication. Treatment of patients with impending coma or coma is related to removal of substances concerned with formation of ammonia or interference with toxicity of ammonia already present. Prophylactically, ammonium compounds, narcotics, and barbiturates should be used with caution. Care must be taken with paracenteses, diarrhea, and diuretic administration because of possible relation to electrolyte imbalance. Removal of all nitrogenous substances from the intestine regardless of the causative factors is the first step in active treatment. Purging of the gut to remove any blood is indicated; and dietary control of protein intake is mandatory. Concomitant administration of antibiotics is reasonable in order to decrease intestinal bacterial action. Neomycin—daily dose of 6 gm in acute cases and 4 gm in chronic cases—appears to be the drug of choice. Because of renal and auditory toxicity dosage, adjustment or even cessation may be required occasionally.

Rationale of glutamic acid therapy is based on the combination of sodium glutamate with ammonia to form glutamine which transports ammonia to the kidney and by transamination with pyruvic acid to form alphaketoglutaric acid. Variable results from use—25 to 50 gm daily IV—have resulted in the recommendation for use in selected cases only. Arginine, ornithine, and other comparable substances also have been recommended because of their activity in the urea cycle. Again, the results have not been uniform and they are not recommended for routine use.

Massive doses of steroids have recently been reported to effect a remission from coma. As much as 250 mg four times a day has been used for short periods. In acute hepatitis with coma due to extensive necrosis, their use may be of value. (S. Reichman, Current Management of the Pathophysiological Disorders in Cirrhosis and Hepatitis: *Amer J Med Sci*, 239: 642-654, May 1960)

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### Pelvic Pain in Women

In females, it has been customary to regard all pain located between the umbilicus and the knees as originating in the genitalia, especially if it occurs with, or is exacerbated by, the menstrual period. Even if the genitalia are normal, the idea is so ingrained that pelvic pain arises from the genitalia that if disease cannot be found, it is invented. Today, the "cystic" ovary is favored; the era of the retroverted uterus is receding.

The desire to eliminate pelvic pain motivates more gynecologic surgery than any other single cause. Many asymptomatic small myomas and cysts on the ovary are removed and suspensions of the uterus done merely because the physician knows the patient has pain—and he does not know what is causing it. Once the abdomen is opened at an exploratory operation, it takes more

courage than most men possess to refrain from excising something. For a couple of months after the operation the patient won't have pain because the doctor's personality and the events of the operation occupy her mind for this length of time; but, if something has been removed and the patient has recurrence of the pain, she can always believe that the physician didn't take out the right thing or didn't take out enough. By the time a gynecologic consultant sees the patient, she has a battle-scarred abdomen, she has lost her appendix, her uterus has been suspended, and she still has pelvic pain.

Pelvic pain may be divided into two major groups—pain which definitely arises from the genitalia and that which does not. The latter includes pelvic neurosis; pelvic bone, joint, and muscle dysfunction; and diseases of other intrapelvic structures, such as urinary tract and bowel.

Few of the female genitalia actually have end organs for pain—the vulva, vagina, and the visceral and parietal peritoneum that covers the various organs. The ovary has no means to convey the sensation of pain directly; all pain from this organ is mediated and referred.

### Pain of Intragenital Origin

Irritation. Irritation as a cause of pelvic pain is simple to understand. There are a variety of causes for this type of pain, among which is the common pelvic inflammatory disease. Other causes might be degeneration of a myoma, extrusion of the contents of a tumor into the abdominal cavity, rupture of the bladder with extrusion of urine, or hemorrhage into the pelvic cavity. Probably, the most common source of irritation with which the gynecologist deals is the latter. Experiments have shown that when fullness, aching, pain, and tenderness persist or recur, hemorrhage in the peritoneal cavity either is persisting or has recurred. Fever usually occurs only when the amount of blood in the peritoneal cavity exceeds 400 ml; leukocytosis is not marked.

Traction. It is well known that traction on a mesentery causes pain. Genital prolapse may produce traction, not on a mesentery, but on the supports of the uterus which in turn produce enough pulling on the parietal peritoneum and on the peritoneum covering the uterine supports to produce a peritoneal type of pain. Torsion of a tumor may produce pain of this type. Generally speaking, it is the smaller tumor that twists. Rather than a pulling sensation, pain in this case is a matter of interference with blood supply. Probably the nerves accompanying the blood vessels are responsible for the pain.

Distention of Viscus or Tissue Space. A primary fact is that slow distention of a cyst or the urinary bladder does not cause pain; rapid distention does.

Pressure. The author is skeptical that pressure in obstetric and gynecologic matters ever produces pain. In growth of cysts and other tumors, resultant pain is conceived to be due to traction.

Rupture of a Viscus. The exact mechanism of production of pain in this phenomenon is not clear. It is not as a result of muscle or peritoneum tearing, but probably from introduction of blood or other foreign substance into the peritoneal cavity.

### Pain of Extragenital Origin

The author believes that the greatest single cause of pelvic pain of extragenital origin is pelvic neurosis. When one considers that the gynecologist deals with one of the two major drives of human existence, one can recognize that aberrations can easily produce neurosis. Women's psyche is much more closely attuned to her genital apparatus than is the male psyche.

Dysfunction of bone, joints, urinary tract and bowel is responsible in a small way for a certain amount of pelvic pain. The history is usually extremely difficult to elicit. How much easier to operate for a small myoma, even if it produces no symptoms.

In the case of a patient with chronic pelvic pain in which every diagnostic procedure has been exhausted and nothing abnormal can be found, exploration is indicated. The author contends that the patient should be told ahead of time that nothing is wrong with her genitalia, but that physicians are fallible and a search is going to be made to be sure nothing has been overlooked. If no pathology is found, nothing should be removed. Under these circumstances, exploratory laparotomy is justifiable.

The cause of pelvic pain cannot always be diagnosed. However, surgery can be refused when no true pelvic lesion is found. Only in this way can neurotic fixations and chronic pelvic invalidism which is so common in women be avoided. (W. F. Mengert, Pelvic Pain in Women: Postgrad Med, 27: 716-722, June 1960)

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### Chemical Osteosynthesis

Chemical osteosynthesis by means of a polyurethane polymer, Ostamer, was described in 1958. The chemical, a prepolymer, and a catalyst, were mixed at the time of surgery and the resulting liquid polymer poured into a prepared bone cavity. The chemical reaction caused the polymer to foam and expand, fill the cavities, and bond to the bone surfaces. The plastic foam set in 15 to 20 minutes and completely hardened 24 to 48 hours later. Weight-bearing or functional use was then permitted. Experimental studies in dogs demonstrated replacement of the polymer by new bone within 18 to 24 months, its lacunar structure providing a framework for endochondral bone proliferation. No evidence of local or systemic toxicity was observed.

The author reports use of Ostamer fixation in a variety of orthopedic and traumatic conditions; 50 operations were performed on 41 patients.

Conventional approaches were employed and tourniquets used when possible. Diaphyseal lesions were fixed by removing cortical strips of varying lengths from each fragment with a motor saw and hollowing the medullary cavity which was then filled with Ostamer. Metaphyseal fixation required removal of a cortical strip from the diaphyseal fragment, cavitation of the epiphyseal fragment, and filling of the defect with the material. Details of preparation of other particular joints or bones are given.

The manufacturer's instructions for preparation of Ostamer were carefully followed. Complete fixation of bone fragments was determined by gentle movement of the limb before the wound was closed. Patients were immobilized postoperatively by plaster of paris or traction for a period of several days to 2 weeks. In some cases, because of apparent precarious fixation or subsequent failure of fixation, immobilization was continued for several months in an effort to obtain bony union. As a rule, weight-bearing or functional use was permitted as soon as wound healing occurred.

The period of postoperative observation extended from a maximum of 7 months to a minimum of 6 weeks. Fixation was considered successful if there was x-ray evidence of bony union by callus; failure, if any motion developed postoperatively. Maintenance of fixation without x-ray evidence of bony union was considered to be of undetermined status, capable of uniting or breaking at any time. By these standards, 8 cases have been successful, 15 have failed, and 27 are still undetermined.

Of 11 operations on the long bone of the upper extremity, 7 have healed by subperiosteal callus formation and the remaining 4 are apparently holding, though ununited. Conversely, only one of 18 operations of the long bone of the lower extremity has united by callus formation, and 6 are still in an undetermined category. Eleven are known failures of fixation.

Four arthrodeses have failed; the remaining 15 are apparently holding, but do not show x-ray evidence of bony union.

The Ostamer column was discovered to have broken completely across at the fracture site in 4 patients. Failures of this type are due to insufficient strength of the material. They can probably be prevented by imbedding metallic reinforcement across the fracture site. The Ostamer column pulled away from the bone cavity in 11 patients.

It is significant that 14 of the 15 failures occurred in weight bearing locations.

Wound infection of varying severity developed at different postoperative intervals in 12 patients. Seven involved arthrodeses; one, fixation of a displaced fracture of the neck of the humerus; 3, fixation of the upper end of the tibia and lower end of the femur; and the remaining one, stabilization of a pathologic fracture of the mandible due to multiple myeloma. Three factors are believed to have contributed to this high incidence of infection: (1) apparent

foreign body reaction of Ostamer when it becomes loose in the bone; (2) necessity for extensive bone excavation; and (3) contamination by a carrier member of the operative group.

There has not been evidence of local tissue reaction in any cases healing by primary intention, and no evidence of systemic toxicity.

Specimens of Ostamer were removed from 6 reoperated patients and studied microscopically. Most sections from bone contact areas showed some degree of fibroblastic proliferation within the Ostamer lacunas. There was no evidence of osteoblastic activity in the more central portions of the Ostamer, even as late as 4 months postoperatively. It appears that many years of observation will be necessary to determine the ultimate fate of the imbedded material.

The advantages of immediate bone fixation and restoration of function that may be obtained by this method warrant further study in selected patients. On the basis of the author's experience, the best prospects for success appear to be in fixation of the long bones of the upper extremity and the subastragalar and ankle joints. (B. W. Drompp, Chemical Osteosynthesis of Fractures and Non-Unions of the Shafts of Long Bones of the Lower Extremity: Papers of The American Association for the Surgery of Trauma, 733-744, 1959)

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#### Dextran Therapy in Severe Burns

In 1954, experience was reported suggesting that dextran was an effective agent for prevention and treatment of burn shock and was free of serious reactions. Since that report the author's policy of treatment has emphasized dextran for colloid replacement. Dextran and blood in approximately 2:1 ratio for burns generally exceeding 25% of body surface area—and, with significant third degree burn—has been employed. For most burns approximating 20% of body surface area, emphasis has been placed upon dextran as the sole colloid for blood volume replacement.

Dextran, a polymer of glucose, was used by the author as a 6% solution in saline, and had an average molecular weight approximating 70,000. The substance acts as a plasma volume expander by virtue of its osmotic pressure effects. Extensive use during the Korean conflict demonstrated that it had considerable usefulness in managing shock seen in battle casualties.

#### Mortality According to Percentage of Burn

	Body Surface Area (%)		
	1-25	26-50	51-100
Adults (over 12 years)	32	67	97
Children	13	58	94

The 246 patients in the study ranged in age from 6 months to 95 years, and were equally divided by sex. The area of burn varied from 8 to 100% and many patients had significant third degree burn.

Dextran has been given in amounts up to 6000 ml during the first 48 hours after injury. Characteristically, the initial response to dextran infusion has been good as evidenced by circulatory improvement. Although many patients received whole blood, the majority were treated initially with dextran. The efficacy of the shock therapy is attested to by the fact that only 9 patients in the series died during the first 2 days after injury.

Renal function following dextran therapy has been satisfactory. Urinary output has been well maintained, and blood urea nitrogen has rarely been elevated during the first 2 days. The patient with a successfully treated burn ordinarily excretes 25 to 50 ml or more of urine hourly during the 2 days following injury; dextran has been most helpful in maintaining this output. In many instances, infusion of 500 ml of dextran in 30 minutes to an oliguric patient resulted in increased urinary volume. This response has been a helpful test in differentiating oliguria due to hypovolemia from that due to renal damage. Renal failure was seen infrequently and was usually associated with prolonged hypotension. No untoward effects on the kidney due to dextran therapy, either clinically or pathologically, were observed.

Because dextran may produce interference with typing and crossmatching of blood, a blood sample was drawn before dextran was given. However, retyping after dextran presented no serious difficulty, and no major reaction to transfusion developed.

Serum protein levels fell routinely following dextran therapy with a level of around 4.5 gm% not being uncommon. These values approached normal as dextran was eliminated. Although fall in serum protein is largely a phenomenon of dilution, there is some evidence to suggest that serum albumin may actually leave the circulation after dextran therapy. The serum globulin level recovered more rapidly than the serum albumin level, probably due to increased production of antibodies. Wound healing in experimental animals is not delayed by dextran.

Anaphylactic reactions—itching, urticaria, pain in joints, respiratory distress and vasomotor collapse—have been reported following administration of dextran to normal human volunteers. No patient in the author's series showed evidence of any allergic reaction. It may be that the body's response to injury protects the patient from allergic reactions.

Studies in human volunteers have demonstrated that dextran may produce prolonged bleeding. This may be due to coating of platelets by dextran, thus interfering with their disintegration and release of thromboplastin. On this basis, the safety of dextran has been seriously questioned.

Of the 246 patients, prolonged bleeding from some route was observed in 18. Bleeding was evidenced chiefly by blood in vomitus or tarry stools and, with one exception, was not massive. Of the patients examined, none

demonstrated prolonged bleeding time. Controlled studies confirmed this observation. Therefore, it may be concluded that dextran does not produce significant bleeding in patients with severe burns. Apparently, the burned patient is protected in some manner from the prolonged bleeding seen in normal human volunteers. (B. W. Haynes Jr, Dextran Therapy in Severe Burns: The American Association for the Surgery of Trauma, 684-689, 1959)

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RADM Hogan, USN

I take this opportunity to endorse the Chief, Bureau of Medicine and Surgery's article on the importance of physical fitness in our Navy which appears here. It is of paramount importance for all officers to realize that even the best trained men will not perform efficiently unless they are physically and mentally fit.

A handwritten signature in dark ink, appearing to read "W. R. Smedberg III". The signature is written in a cursive style with a horizontal line at the end.

W. R. Smedberg III  
Chief of Naval Personnel

The Importance of Physical Fitness in the Navy  
RADM B. W. Hogan MC USN

The American way of life today has become much easier and more comfortable because of the widespread use of labor-saving devices and other recent developments. Life in the Navy has likewise been made easier, more comfortable, and has provided more leisure time for our personnel. Naval personnel participated in a great deal of physical exercise in the performance of their routine duties before the widespread use of many of the labor-saving devices currently found in the Navy. At the present time there is a tendency for many personnel in the Navy not to participate in a regular physical exercise program and, as a result, there has been a deterioration of the physical fitness of some individuals.

The effectiveness of naval personnel in the performance of their duties depends primarily on their knowledge, ability to reason, and application of their skills and capabilities rather than their physical attributes. However, it is widely recognized that physical fitness, coordination, and stamina are important factors in job efficiency.

Appropriate physical exercise produces many positive and desirable effects for personnel in the Naval Service. The feeling of relaxation enjoyed by an individual after participating in guided physical exercise is one of the

beneficial physiological results of such a program. This will usually permit him to divorce himself temporarily from the stress and strain of his regular work. This desirable effect of exercise will frequently provide a means for increased efficiency in his job. Many persons in this country tend to use alcoholic beverages as their principal means of relaxation and of getting away from the realities of the stress, strain, and tension of their work. It has been well demonstrated in the medical literature that an excessive consumption of alcohol over a prolonged period of time is detrimental to an individual's physical and mental health and will lead to a decreased efficiency in his job.

It is impossible to lay down hard and fast rules about exercise for everyone of a certain age because no two persons have exactly the same physical needs or psychological preferences and also because physiological and chronological ages are not the same. Some individuals will live to an old age and will be free from disease despite the fact that the only exercise they get is in breathing, talking, eating, and tending to their other physiological processes.

Certain disease processes preclude strenuous and prolonged physical exercise. Most naval personnel enjoy basically sound health and appropriate physical exercise will usually prove beneficial.

Physical exercise at any age should be a more or less planned, but not boring or burdensome, program. The type of exercise performed is not particularly important, but it should be to the liking of the individual and should suit his aptitude, muscular strength, and capability. The strenuousness and duration of the physical exercise should vary in accordance with the general physical condition, the desires, and the physical abilities of the participant. A healthy person who has been long accustomed to vigorous exercise can usually continue to exercise, but it is usually advisable to tone down the energy expended and the amount of time spent in exercising with increasing chronological, and particularly physiological, age.

The majority of naval personnel eat much the same diet, drink and smoke moderately, participate in some exercise and gain approximately 20 to 25 pounds of body weight in a course of 30 years, or a period representing a naval career. With increasing age there is a tendency for muscle mass to be replaced by fatty tissue. Medical authorities feel that excessive overweight is a deterrent to longevity and to good health. Obesity, or excessive body weight, is caused by the combined effects of overnutrition, heredity, and other factors. Obesity is an important factor in the development of numerous degenerative diseases. Obesity should be avoided by restricting the total caloric intake. The diet should be well-balanced in order that all the necessary components, including proteins, carbohydrates, fats, vitamins, and minerals are provided for the proper maintenance of good health and nutrition. In other words, starvation diets are not recommended for the purpose of weight reduction. Personnel who have a problem of obesity should consult their medical officer concerning the ideal diet to help that individual reduce his body weight. Physical exercise exerts a desirable effect in assisting in the

control of obesity in many individuals. Without a reduction in caloric intake the increased metabolic requirement resulting from physical exercise may help to control body weight in an obese individual. Obesity is best treated by a reduction in the caloric intake in conjunction with appropriate physical exercise, both under the supervision of a medical officer.

Physical exercise has positive effects on the individual's health, including the maintenance and establishment of good muscular tone throughout the body, and this includes the muscle of the heart. The leg muscles become stronger if the individual participates in tennis, golfing, cycling, or long walks, whereas the arm muscles are affected by exercises such as woodcutting, swimming, and gardening. Good muscle tone provides numerous benefits to the individual, one of which concerns the circulation of the blood. The heart is a most important factor but is not the sole supporter of the circulation. The elasticity of the aorta and great vessels and the proper functioning of the smaller vessels are important in providing an even flow of blood to the various organs of the body. The veins with their valves act as local pumps for the return of blood to the heart when they are compressed by the muscles which surround them. The better the muscle tone the better is this support to the heart by the veins.

Properly conducted physical exercise will usually produce a beneficial effect on the individual's psyche. Most people, old and young, are helped by the relaxation which comes from correct exercise, usually midway in amount and intensity between the extremes of triviality and of exhaustion. For many persons exercise is a stimulating antidote for nervous tension, stress, anxiety, and mental concentration. A moderate fatigue of skeletal muscles often gives the individual peaceful sleep, a sense of equanimity, and mental repose.

Physical exercise is beneficial to the function of the digestive tract probably by reducing nervous tension and stress, which are important factors in many diseases of the gastrointestinal tract, such as peptic ulcer, irritable colon syndrome, cardiospasm, and others. Physical exercise also exerts a favorable effect on the physiological function of the bowel.

Physical exercise is beneficial in improving the functions of the respiratory organs. Almost any type of vigorous exercise or even repeated deep breathing exercises improves the tone of the diaphragm muscles. Good tone of the diaphragm with wide respiratory excursion not only aids respiration but also improves the diaphragm's pumping action, thus aiding in the suction of blood back to the heart. The deepening of respiration which comes with exercise favors the function of the lungs in gaseous exchange and in the condition of the lung tissue itself. Certain diseases of the lungs with which there is a loss of elasticity of the lung tissue, such as bronchitis and emphysema, may develop with advancing age and may limit the amount and duration of exercise possible, but these conditions do not, as a rule, preclude in themselves mild exercise within the reserve of the individual.

The medical benefits of physical exercise have been consistently demonstrated during recent years by early ambulation of patients who have had major surgical operations, various types of injuries, certain types of medical illnesses, or patients who have delivered a baby. In the past many of these patients were kept at bed rest for prolonged periods of time, and the convalescent and recovery periods were much longer while the incidence of complications was much higher as compared to our present early ambulation method of treatment. By encouraging physical activities shortly after surgery, injury, or delivery, the patient retains good muscle tone, improved circulation, and good respiratory function, resulting in a speedier recovery and fewer complications.

Exercise of almost any kind, suitable in degree and duration for the particular individual concerned, plays a useful role in maintaining the individual and in promoting a state of good health. It is impossible to lay down hard and fast rules for physical exercise for all naval personnel because each person requires individual appraisal.

All personnel of the Navy will benefit by participating in an appropriate physical exercise program in accordance with the individual's desires, and commensurate with his physical capabilities, strength, and stamina. For those who have a problem of obesity, the appropriate physical exercise program should be coordinated with a reduced caloric intake diet, both under the supervision of a medical officer. (Naval Training Bulletin, 1-4, Spring 1960)

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BUMED INSTRUCTION 6010.12

11 July 1960

Subj: Motion sickness; evaluation of cases prior to transfer to hospitals for disposition

To reduce the length of hospital stay for patients with the diagnosis of chronic motion sickness, occurring at sea, extensive and thorough evaluation as well as substantiation of extent of impairment of function shall be prepared before effecting transfer to a hospital for disposition.

BUMED INSTRUCTION 6530.7

12 July 1960

Subj: Serum from burned patients

Investigation of the hypothesis that convalescent serum from acutely burned patients contains an antitoxin which may be therapeutically effective in treatment of burned patients is being undertaken by the Tissue Bank Department of the Naval Medical School. In view of the life-saving potential involved, widespread cooperation in submission of samples of serum is urged. Procedure for collecting and submitting such samples is outlined.

Recent Research ReportsU. S. Naval Medical Research Unit No. 3, Cairo, Egypt

1. Isolation of Phlebotomous Fever Virus from Phlebotomus Papatasi. MR 005.09-1202.5.01, February 1960.
2. Furazolidone Therapy in Typhoid Fever. MR 005.12-1001.16.01, June 1960.

U. S. Naval Dental Research Facility, Great Lakes, Ill.

1. Evaluation of a Panoramic Dental X-Ray Machine. Project 6-59-04-049.105 (a), April 1960.

U. S. Naval School of Aviation Medicine, NAS, Pensacola, Fla.

1. Factor Analysis of Selection Tests and Performance Measures in U. S. Naval School, Pre-Flight. MR 005.13-3003, Subtask No. 10, Report No. 2, 18 August 1959.
2. The Officer Selection Battery as an Adjunct to the Naval Aviation Selection Battery. MR 005.13-3003, Subtask No.1, Report No. 31, 15 October 1959.
3. Factor Analysis of Aptitude and Achievement Tests and Performance in the Naval Air Training Program. MR 005.13-3003, Subtask No. 10, Report No. 3, 16 October 1959.
4. The Postural Sway Test and Its Correlations. MR 005.13-3001, Subtask No.7, Report No. 3, 12 November 1959.
5. The Temporal Lag Between Alveolar Pressure and Resultant Mouth Air-flow (Pressure-Flow Lag (PFL) Phenomenon) and Its Variation with Gas Density, Breathing Effort, and Breathing Frequency. MR 005.13-3100, Subtask No. 2, Report No. 1, 15 November 1959.
6. The Separation of Serum Proteins by Density Gradient Electrophoresis. MR 005.12-1004, Subtask No. 2, Report No. 3, 25 November 1959.
7. Loss of Counter-Rolling of the Eyes in Three Persons Presumably Without Functional Otolith Organs. MR 005.13-6001, Subtask No. 1, Report No. 50, 15 December 1959.
8. A Measure of Cultural Background. MR 005.13-3003, Subtask No. 2, Report No. 3, 16 December 1959.
9. Ballistocardiographic Evaluation of the Cardiovascular Aging Process in Overtly Healthy Males Aged 18 - 54. MR 005.13-7004, Subtask No. 6, Report No. 7, 31 December 1959.
10. An Apparatus for the Determination of the Respiratory Exchange Ratio (R) and Metabolic Rate of Laboratory Animals. MR 005.13-3100, Subtask No. 4, Report No. 1, 1 January 1960.
11. Gross Effects of Liquid O<sub>2</sub> Contaminants. MR 005.13-3100, Subtask No. 7, Report No. 1, 9 January 1960.
12. Test of New Rationale and Methodology for the Forced-Choice Technique. MR 005.13-5001, Subtask No. 1, Report No. 21, 1 March 1960.

From the Note Book

American Podiatry Association Meeting. The American Podiatry Association will conduct its annual meeting at the Drake Hotel, Chicago, 25 - 30 August 1960. A military section will be presented by members of the Armed Forces on the afternoon of the 28th. Eligible inactive Naval Reserve Medical Department officers may receive credit for one retirement point, provided their attendance at this section is registered with the military representative present.

Aviation Medicine Class Convenes. Class No. 95, the largest in the history of the school, convened 11 July 1960 at the Naval School of Aviation Medicine, Pensacola, Fla., beginning a 24-week period of postgraduate instruction in medical specialties and operational aspects of aviation medicine. Upon completion of their medical training phase, the students will receive indoctrination flight training prior to being designated Naval flight surgeons. Of the class of 47, one officer-student is from the Indonesian Navy, one from the French Navy, and three from the U.S. Army. (PIO, NAVSCHAVMED)

ADM James Becomes Executive Director of ICS. On 1 July 1960, RADM Walter F. James MC USN (Ret) became the Executive Director of the International College of Surgeons. Recently retired after 34 years of active duty, ADM James succeeds the late RADM Ross T. McIntire in the appointment.

FAA Appreciation. E. R. Quesada, Administrator of the Federal Aviation Agency, told a committee of the U.S. Senate, "The Navy has offered use of its training facilities at Pensacola. One of our doctors has already completed this training. Military medical officers with a background in aviation medicine have been very helpful in the current FAA program."

Renal Ablation Hypertension. Studying the effects of dietary alterations in relation to development of hypertension following renal ablation, the authors demonstrated that salt is highly injurious when administered to animals with three-fourths renal ablation. The action of salt may be independent of elaboration of hormonal agents by the renal stump. It is suggested that renal ablation hypertension has the same mode of origin as salt hypertension and is related to disturbances in electrolyte and water metabolism. (S. Koletsky, A. Goodsitt, Arch Path, June 1960)

Antiemetic Effects of Trimethobenzamide. Apparently acting selectively on the vomiting center, trimethobenzamide (Tigan) gives indication of being a most effective antiemetic. The complete lack of side effects or toxicity makes it a valuable addition for treatment of the distressing symptoms of nausea and vomiting incident to a variety of conditions or diseases. (A. Kolodny, Amer J Med Sci, June 1960)

Growth Controlling Hormone. The author presents a report on a new quality of young bone marrow: the capacity to regulate the normal growth of mammals and to prevent pathologic growth of malignant tumors. He demonstrates by illustrations the dwarfing of animals (goats and a calf) deprived of the marrow of the femur, tibia, humerus, and ulna, and also the increase in growth of the whole bodies of white mice treated by injections of an extract from young bone marrow. Current knowledge of the nature and mechanism of growth is summarized, and the author makes available to the profession his promising experience in fighting carcinoma, asking that his results with a special powerful extract be verified by others. (P. Rosenstein, J Int Coll Surg, June 1960)

Influence of Antibiotics on Spread of Tumors of Colon. Conducting controlled experiments on tumor transplants in animals, the authors observed that tumor cells spilled into the peritoneal cavity during an open anastomosis of the colon will grow in various areas in the peritoneal cavity. In this and other reported experiments, it was observed that control of bacterial flora of the colon increased the incidence of tumor growth in the anastomosis. (I. Cohn Jr, M. Atik, Ann Surg, June 1960)

Colorimetric Urine Test for Pheochromocytoma. A rapid and simple chemical technique for screening hypertensive subjects for presence of pheochromocytoma is described. The test differentiates between normal subjects or patients with primary hypertension and patients with pheochromocytoma. A negative result requires no further study whereas a positive one necessitates confirmation. (S. Gitlow, et al, Amer J Med, June 1960)

Transfusion and Cardiac Arrest. Analysis of 157 cases of cardiac arrest led to the conclusion that in 50 the sole cause was massive transfusion of hyperpotassemic bank blood. Serum potassium concentrations increase progressively in bank blood, and hemorrhage increases the susceptibility of the body to potassium. These considerations are of fundamental importance in avoiding cardiac arrest and in treating it when it occurs. (H. LeVeen, et al, JAMA, June 18, 1960)

Uropepsin Excretion in GI Bleeding. Two-hour uropepsin excretion was studied in patients with gross gastrointestinal hemorrhage. While the overlap of results was considerable among the patients with different etiologies for bleeding, a high excretion was found to be highly suggestive of duodenal ulcer disease—47% of the duodenal ulcer cases exceeded the normal range. The test proved to be more valuable in differentiating variceal bleeding. It was concluded that the test was of limited though definite value in differential diagnosis of the cause of gastrointestinal hemorrhage, particularly in conjunction with other laboratory tests. (A. Cummins, Ann Int Med, June 1960)

**DENTAL****SECTION**Education for the Professions

The increasing complexity of civilization has made the role of the professional man more difficult than before. He must wear "two hats." He is not only the practitioner of his art, but he also is looked on as a leader of thought and action in local and national affairs. The men of the professions are guardians of human values.

There is little doubt of the shortage of professional men in the United States. In 1930, there were 58 dentists per 100,000 population. The number of active dentists per 100,000 persons will fall to 43 by 1975 if population continues to increase at predicted rates. Without additional training facilities it is expected that there will be a national deficit of 35,000 dentists by 1975. Demands for dental care undoubtedly will increase with improved economic conditions, and the shortage by 1975 will be even more serious than the figures indicate. This situation must be corrected if we are to have a standard of dental care comparable to our standard of living.

Forty-seven dental schools now are in operation, and plans exist for opening several more schools. Many schools undoubtedly will expand their facilities to accommodate more students.

The emphasis placed by the dental profession on advanced educational programs is an indication of the efforts being made to maintain a vigorous profession. There are over 375 graduate and postgraduate programs offered by the nation's dental schools, an increase of almost 80% in the last five years. In addition, nearly all dental schools offer short refresher courses. Many dentists take advantage of the opportunities offered by these programs.

Dentistry is seizing the opportunities for research. However, a comparison of the \$210,000,000 spent annually on tooth pastes and tooth powders with the \$10,000,000 voted by the Senate for activities of the National Institute of Dental Health this year leaves much to be desired. The success of fluoridation indicates the results which can be achieved through adequate research. Yet much remains to be done. Three out of four persons in the United States have an oral disorder of some type, and tooth decay affects 95% of the population. Dental disease is a national problem which costs the public over \$1,750,000,000 for dental care each year. Research can help correct this situation.

The professional man must prepare himself to be a responsible citizen and leader. Far-reaching changes are taking place in the world every day,

and it is incumbent on the dentist, physician, and lawyer to know about these changes if the professional men are to continue to wear the mantle of leadership. "We are not put into this world to sit still and know; we are put into it to act." (Senator J. William Fulbright, Arkansas Dental Journal, 30: 4-6, September 1959)

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### Extension Course in Prosthodontics

A home study extension course in complete denture prosthesis (Prosthodontics, Part I, NavPers 10763) is now available to Dental officers of the U.S. Navy and Naval Reserve. Developed by the staff of the U.S. Naval Dental School with the assistance of professional test writers of the Home Study Department of the University of Chicago, the course is comprised of six assignments:

(I) Importance of accurate diagnosis, prognosis, and treatment planning; anatomic and physiologic factors involved in complete denture construction; and surgical factors involved in preparing a patient for complete dentures; (II) principles and techniques of impression making for complete dentures; (III) principles and techniques for establishing and recording maxillomandibular relations; (IV) principles and techniques for selection and arrangement of teeth to insure good esthetic effect and proper occlusion; (V) review of waxing, flasking, and processing procedures; remounting of finished dentures; perfecting occlusion; repair, duplicating, and rebasing of complete dentures; problems of constructing a complete maxillary denture against natural mandibular teeth; and advantages and disadvantages of the cast gold base; (VI) technique for immediate denture service.

Included in the course material is a recent edition of a widely accepted complete denture textbook. The textbook and outline provide a framework of information for review and study in the field of complete denture construction.

This is the fifth in a series of postgraduate level extension courses prepared by the Dental School to augment the continuing education program of the Naval Dental Corps. Courses previously announced are Endodontics, NavPers 10407; Oral Diagnosis, NavPers 10739; Oral Surgery, NavPers 10729; and Prosthodontics, Part II, Partial Denture Prosthesis, NavPers 10764. Other courses, covering crown and bridge prosthesis, operative dentistry, and periodontics are planned.

These courses are intended to provide Navy Dental officers, especially those at sea or at remote stations, with a balanced educational program. They are not intended to replace short postgraduate courses, graduate courses, residency training, or the many excellent educational experiences now enjoyed by officers of the Dental Corps.

Reserve Dental officers may receive promotion and retirement points to be credited at the successful completion of each course or course unit. Unit one of Prosthodontics, Part I, is comprised of Assignments I through IV and is evaluated at twelve points; unit two, Assignments V and VI, is evaluated at six points.

Applications for enrollment should be submitted on NavPers 992, Application for Enrollment in Officer Correspondence Course, via official channels to the Commanding Officer (Code 5), U.S. Naval Dental School, National Naval Medical Center, Bethesda 14, Md.

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#### Accuracy of X-Ray Timers - A Trial Investigation

In dental roentgenography, radiation reaching the patient can be reduced greatly by reducing the exposure time. This is achieved by using film with a higher emulsion speed. The faster film, however, is not always satisfactory; sometimes the resulting roentgenograms are inferior in quality and exhibit variance in their densities. The primary reasons for these defects are fog and inadequacy of x-ray timers.

Timers on the 53 dental x-ray units in the offices of dentists in the Philadelphia area were checked for accuracy; 45 (85%) were inaccurate; 29 (55%) were too fast so that less radiation was being produced than the timer indicated; 16 (30%) were too slow so that more radiation was being produced than anticipated. Timers that were too fast resulted in underexposed film; timers that were too slow, in overexposed film.

If the timer is fast, it is probable that a longer exposure could be used than is recommended by the manufacturer. If the timer is slow, it may be necessary to use a lower speed film at the 8-inch target-film distance; or if the high-speed film is used, the milliamperage can be lowered from 10 ma (the usual operating level) to 5 ma. Since the density of the film is controlled primarily by milliamperage seconds (milliamperage x seconds of exposure), the reduction in milliamperage compensates for the inaccuracy of the timer.

The timers on five newly manufactured 90 KVP (kilovolt peak) dental x-ray machines were examined and found to be highly accurate at all fractional second exposures. (W.J. Updegrave, R. L. Mohr, A.J. Potts, Oral Surg, 12: 717-722, June 1959)

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#### ACD Answers on Ethics

A report published in the April 1960 issue of the American College of Dentists (ACD) Reporter contained the following questions and answers on the subject of "conduct" in relation to the ethics of dentists. Even though

these are specific guides for Fellows in the ACD, the guidelines set forth should be observed by all dentists.

Q. May a Fellow present papers or articles to dental laboratory groups?

A. Cooperation with dental laboratories is very important, so that the technicians will be directed in their efforts and know what is expected of them. The subject of material of such discussions should pinpoint laboratory technique and not the treatment of the patient. There might be circumstances where a published article would be in order. However, if the objective is to stress basic technical procedures and not "Jones" technique, an article with "Jones'" name attached is hardly necessary.

Q. May a Fellow participate as a teacher by reading papers or furnishing material in courses sponsored by laboratory associations?

A. If such courses are intended to supply basic information to laboratory technicians, the source of such information is logically the dental profession and the dental educational institutions. If such courses are intended as instruction to the dental profession by the laboratory technicians, then the course is out of order since a laboratory or its organization is not recognized as a teaching institution. Teaching institutions and recognized dental societies should plan and sponsor courses of instruction for laboratory technicians in the interest of better understanding of the responsibilities not only of the laboratory and its technicians, but also of the dentist who uses them.

Q. May a Fellow participate as an essayist or instructor in programs for dental assistants including programs for the certification of dental assistants?

A. When such programs are sponsored by the dental society or approved by it, there would be no objection to such activity. He would be cooperating in the society's program in such instances. If the activity did not have the society's approval, it would seem out of order.

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#### Personnel and Professional Notes

LT Hellman to Serve on SS HOPE. LT Stanley M. Hellman DC USNR has been selected as one of two dentists who will serve on board the mercy ship, SS HOPE, for a period of one year. The HOPE will depart San Francisco in September for Indonesia where medical and dental care will be administered to needy persons of that country. LT Hellman, born and educated in Chicago, Ill., was graduated from the University of Illinois College of Dentistry in June 1958, entered the Navy in July 1958, has served aboard the USS SIERRA since June 1959, and will be released from active duty during July 1960.

Dr's Arnim and Chilton Present Lectures at NDS. Sumter Arnim B. A., D. D. S., Ph. D., Professor of Pathology and Director of the Postgraduate School of Dentistry, University of Texas Branch, Houston, Texas; and Neal W. Chilton, D. D. S., M. S., Research Associate in Biostatistics, Columbia University Faculty of Medicine, were recent guests in the special lecture series of the Naval Dental School. Speaking before Dental officers of the Armed Forces, civilian dentists and other interested scientific personnel of the Washington, D. C. area, Dr. Arnim discussed practical techniques and principles in periodontal therapy; Dr. Chilton presented Experimental Design in Clinical Research.

Captain's Hamilton and Swearingen Present Symposium. Captain's T. R. Hamilton and J. C. Swearingen DC USN, U. S. Naval Training Center, Great Lakes, Ill., recently presented a symposium, Mass Casualty Training, before the Outagamie County Dental Society, Appleton, Wis.

Sangley Point Seminar. The 4th annual Sangley Point Dental Seminar, held on 18 June 1960 at the U. S. Naval Station, Sangley Point, Philippines, was attended by many prominent dental practitioners from the Manila area, officers of the Philippine Dental Association, dental educators, and members of the Dental Services of the various Armed Forces in the area. Professional papers presented included: Diagnosis for Complete Dentures—CAPT A. K. Kaires DC USN; The New Approach in Surgical Treatment of Neuralgia of the 5th Cranial Nerve—A. W. deLos Reyes, M. D., D. D. S., F. P. C. S.; Anesthetics in Dentistry—LT R. O. Gibbs DC USNR; Eradicate the Pocket—LT R. D. Ulrey DC USN; Orthodontics—Diagnosis for the General Practitioner—Luz C. Macapanpan, D. M. D., M. S.; and Endodontics—LT R. H. Flagg DC USN.

Deslant Dental Officers Hold Open House. The Destroyer Force, U. S. Atlantic Fleet and the Dental Officers of four Destroyer Force tenders recently were hosts to 81 members of the Rhode Island State Dental Society. The theme for the program concerned the primary reason for existence of the destroyer and destroyer tender. The visiting dentists were welcomed by CDR Grover D. Rawlings USN, Head of Readiness and Training, after which the Dental Officers of the YOSEMITE, GRAND CANYON, YELLOWSTONE, and ARCADIA escorted the visitors through their respective ships and departments. Particular emphasis was placed upon the relationship of the destroyers to the tenders and the tremendous responsibility of the Dental Officer of each tender for the dental health of destroyermen. The visiting dentists observed the modern methods employed to accomplish this important health service. The visitors were extended the privilege of dining in the various enlisted messes of the four ships, and later were provided a tour of the recently rehabilitated and modernized USS PERRY (DD-844). The remainder of the visit was spent aboard the PERRY at sea becoming acquainted with the shipboard routine of the destroyerman.

**RESERVE****SECTION**Uniform Allowances

**Initial Uniform Allowance.** Upon appointment in the Naval Reserve, an officer is entitled to an initial sum not to exceed \$200 as reimbursement for the purchase of required uniforms and equipment. Eligibility to receive this initial sum accrues on the date any one of the three conditions listed below are met. Periods of active duty, active duty for training, or inactive duty training may be counted as duty for the purpose of entitlement only if such duty required the wearing of the uniform. For the purpose of determining entitlement based on inactive duty training, regular drills, equivalent drills, periods of appropriate duty and special inactive duty training may be counted. Eligibility of an officer is determined as follows:

1. Upon the first reporting for active duty as an officer of the Naval Reserve for a period in excess of 90 days on or after 1 January 1953, provided such officer has not heretofore received an initial uniform allowance or uniform gratuity allowance in any amount as an officer under any other prior provision of law; and, provided further, if applicable to the officer concerned, two years have elapsed since separation from active duty as an officer of a Regular component of the Armed Forces; or

2. Upon the first completion of not less than 14 days active duty on or after 1 January 1953 as an officer in the Naval Reserve, or active duty for training with certain unusual exceptions; provided such officer has not heretofore received an initial uniform allowance or uniform gratuity allowance in any amount as an officer under any other prior provisions of law; and provided further, if applicable to the officer concerned, two years have elapsed since separation from active duty as an officer of a Regular component of the Armed Forces; or

3. Upon the first completion of 14 periods of not less than two hours duration each, of inactive duty training after 1 January 1953, as an officer of the Ready Reserve of the Naval Reserve; provided such officer has not heretofore received an initial uniform allowance or uniform gratuity allowance in any amount as an officer under any other prior provision of law; and provided further, if applicable to the officer concerned, two years have elapsed since separation from active duty as an officer of a Regular component of the Armed Forces.

a. **Qualification for Entitlement under Special Circumstances.** The preceding provision in subparagraphs 1, 2, and 3 which requires that at least two years elapse after separation from active duty as an officer of a Regular

component of the Armed Forces would not bar entitlement if a member's duty extended for more than 90 days after the end of the two years limitation notwithstanding that a portion of the duty under the same tour commenced within two years of separation from the regular component.

Additional Active Duty Uniform Allowance. An officer of the Naval Reserve is entitled to a sum not to exceed \$100 as reimbursement for additional uniforms and equipment for performing, or having performed, active duty or active duty for training for a continuous period in excess of 90 days' duration on or after 25 June 1950 at a location where uniforms are required to be worn. Entitlement to this additional active duty allowance is determined as follows:

Officers of the Naval Reserve entering on active duty or active duty for training for a continuous period in excess of 90 days' duration on or after 25 June 1950 at a location where uniforms are required to be worn are entitled, for each time of such entry or re-entry, to a sum of \$100 provided one of the following conditions is met.

1. The period of active duty or active duty for training is the first such period since appointment as an officer in the Naval Reserve, and the officer concerned has not received under any provision of law an initial uniform allowance or gratuity in excess of \$200 incident to, or within a period of two years prior to, entering on that particular tour of active duty or active duty for training.

2. The period of active duty or active duty for training is the first such period since appointment as an officer in the Naval Reserve following a termination of active duty in another branch of the Armed Forces which required a different uniform and the officer concerned has not received, under any provision of law, an initial uniform allowance or gratuity in excess of \$200 incident to the particular tour of active duty or active duty for training on which eligibility is being based, regardless of the fact that he may or may not have received an initial uniform allowance or gratuity of \$200 or less or an additional active duty uniform allowance of \$100 at any time under any provision of law for a prior period of active duty or active duty for training in a Reserve component of another branch of the Armed Forces which required a different uniform.

3. The period of active duty or active duty for training is the second such period after appointment as an officer in the Naval Reserve or any succeeding such period thereafter, and provided a period of at least two years has elapsed since the officer concerned previously completed a period of active duty or active duty for training in excess of 90 days..

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For announcement concerning retirement point credit for attending a military section of the American Podiatry Association's Annual Meeting, see page 22.



## PREVENTIVE MEDICINE

### Blood Dyscrasias Associated with Chloramphenicol (Chloromycetin) Therapy

With an increase in the receipt of reports by the Registry on Blood Dyscrasias in which chloramphenicol is associated with the development of a blood dyscrasia, it becomes important once more to review briefly the toxic effect of this drug on the blood-forming organs of sensitive persons. Paucity of recent publications in the American literature should not be construed to mean that the reports of chloramphenicol-induced aplastic anemia some years ago were merely a chance association. There have been numerous reports in more recent years of chloramphenicol-induced aplastic anemia in the foreign literature. Between January 1953 and January 1960, the Registry on Blood Dyscrasias has received a total of 223 reports of pancytopenia; of these, 91 were cases in which chloramphenicol had been administered. Of the 91 cases, there were 34 instances in which chloramphenicol was reported as being the only drug given.

Severe reactions to antibiotics occurring in patients between late 1955 and early 1957 have recently been studied in a nationwide survey by Welch and colleagues of the Food and Drug Administration, Department of Health, Education, and Welfare. This study reported 31 patients with aplastic anemia associated with chloramphenicol administration of whom 23 died. Of these 31 cases, only 8 had been reported to the Registry. Although some of these patients may have received chloramphenicol in the presence of a developing aplastic anemia, this explanation seems improbable. It is important to note that, in the survey of the FDA, few cases of aplastic anemia were associated with the administration of penicillin, streptomycin, the tetracyclines, or a sulfonamide.

The Subcommittee on Blood Dyscrasias recognizes that chloramphenicol is a valuable and important addition to a physician's armamentarium. This is particularly true since it has been shown that certain strains of staphylococci resistant to penicillin and the tetracyclines are sensitive to chloramphenicol. The manufacturer has repeatedly directed the attention of the medical profession to the need for judicious use of the drug by a warning statement in the labeling and advertising of the product. Although the warning statement specifically cautions against the indiscriminate use of the drug or against its use

for minor infections, examination of the reports received by the Registry reveals that the drug has been used in such conditions as upper respiratory infections—including the common cold, bronchial infections, asthma, sore throat, and tonsillitis—miscellaneous urinary tract and ear infections, undiagnosed low-grade fever, and even disseminated lupus erythematosus, gout, eczema, malaise, and iron deficiency anemia. It is incumbent upon a physician when he prescribes chloramphenicol to carefully weigh the need for the drug in relation to the risk of possible serious toxic effects.

Although the subcommittee recognizes that chloramphenicol is a valuable antibiotic, it is also the opinion of the subcommittee that there is no longer a reasonable doubt that chloramphenicol may cause aplastic anemia. Periodic blood cell counts may be of some help; however, they cannot be relied on to detect signs of marrow toxicity sufficiently early so that chloramphenicol administration can be discontinued before an irreversible aplastic anemia develops. Therefore, judicious use of the drug must be the rule, and it should not be used prophylactically, in trivial infections, or in infections in which other less dangerous antibiotics may be used effectively. (Report of Committee on Research, Council on Drugs, AMA, Blood Dyscrasias Associated with Chloramphenicol (Chloromycetin) Therapy: JAMA, 172: 2044-2045, April 30, 1960)

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#### Recent Advances in the Chemotherapy of Infection

The antibiotic era is a very short one; it encompasses only about 17 years. In a field as young as this, it is difficult to discuss recent specific advances because the whole field is advancing, rapidly in some cases, more slowly in others. As a matter of fact, change has been so rapid that new agents are often widely applied and substituted for the "old" ones about which much still remains to be learned. In some situations progress has come to a halt, and the present lack of success in treatment closely resembles that of the preantibiotic period.

As is often the case, progress creates problems. There is no doubt that the availability of potent antimicrobial agents has solved a great many of the problems in the field of infection. There is also no question that an appreciable number of new problems have been created and that some of these are even more difficult than the old ones. One of the common difficulties today is the large number of anti-infective drugs. There are at present at least 15 antibiotics and 10 sulfonamide compounds. This sometimes creates a difficult dilemma for the physician who must choose a single agent from this large number when he considers such features as degree of effectiveness, route of administration, risk of untoward effects, and cost. The difficulty is even further increased by the availability of mixtures and combinations of

antimicrobial compounds for which claims of superior and inferior activity are simultaneously expressed in the literature.

Substantial advances of clinical significance in the therapy of any disease come only after the drugs which are recommended have been used extensively enough under controlled conditions so that they can be critically evaluated. The development of a new antibiotic, for example, does not necessarily represent an advance in the treatment of infection because the agent may not prove as effective or as harmless as it was first thought to be. In fact, use of the new drug may represent a backward step because it is applied—often very widely—in place of the old agents before it is appreciated that the new drug is not as good as the old one. The price of such an "advance" may be paid by the patient in the hard coin of prolonged illness, serious reactions, and sometimes, even death. In discussing recent advances in the field of antimicrobial therapy it is important, therefore, not only to review the improvements that have come about, but also to discuss some of the poor results and the bad effects of these drugs.

This paper reviews briefly a few selected problems which have practical significance and which illustrate some of the general principles of chemotherapy which, when properly applied, make the difference between effective and poor treatment.

### The "New" Antibiotics

New antimicrobial agents are being developed constantly. Many of these never go beyond the laboratory stage of development because they prove to be too toxic or relatively ineffective. There have appeared in the last several years; however, several new antibiotics and sulfonamides. Among these are ristocetin, vancomycin, kanamycin, amphotericin, sulfamethoxypyridazine, sulfamethoxypyrimidine, and sulfaethylthiadiazole.

Kanamycin (Kantrex). Kanamycin is a water-soluble basic antibiotic obtained as a fermentation product of *Streptomyces kanamyceticus*. It is distinct from, but related closely to, neomycin and has a lesser but definite relationship to streptomycin. It is active against Gram-negative bacteria like *Escherichia coli*, *Aerobacter aerogenes*, and *Salmonella*; Gram-positive organisms, such as *Staphylococcus pyogenes* var. *aureus*; and the tubercle bacillus. It is ineffective against streptococci, *Diplococcus pneumoniae*, and *Clostridium*. In high concentrations the drug is bactericidal, in lower ones bacteriostatic.

Among the untoward effects of the parenteral administration of kanamycin are pain at the site of injection, skin eruptions, damage to the eighth nerve, and nephrotoxicity.

Vancomycin (Vancocin). This antibiotic is active mainly against the B-hemolytic streptococcus, *Strep. fecalis*, *D. pneumoniae*, *N. gonorrhoeae*, *C. diphtheriae*, *Cl. tetani*, and *Staphylococcus*. It is ineffective against all

Gram-negative rods, such as *E. coli*, *A. aerogenes*, *Pseudomonas*, and *Proteus*, and the tubercle bacillus, yeasts, and fungi. The majority of strains of *Staphylococcus* are inhibited by a concentration of 2 mg/ml. Resistance to vancomycin develops in staphylococci only to a very small degree, if at all.

Vancomycin is not absorbed from the gastrointestinal tract and must be administered intravenously to produce the desired clinical effect.

Pain at the site of intravenous injection of vancomycin is relatively frequent. Thrombophlebitis is common, especially in children and adults with small veins. Skin eruptions, usually morbilliform in character, may result from sensitization to the drug. Most patients receiving vancomycin have a large number of hyaline and granular casts and albumin in the urine. Although uncommon, some degree of renal failure with increased serum urea nitrogen and creatinine and decreased PSP excretion may appear when large doses of vancomycin are administered over 2 or more weeks.

Ristocetin (Spontin). The drug is bactericidal at the same level as it is bacteriostatic and is active against Gram-positive cocci including *Staphylococcus*, enterococci, B-hemolytic streptococcus, *Clostridia*, *D. pneumoniae*, *Actinomyces bovis*, *Listeria*, and *Mycobacteria* including the tubercle bacillus. It is said to be especially effective against staphylococci resistant to a variety of other antibiotics.

The main application of ristocetin at present is the treatment of staphylococcal infections produced by strains of organisms insensitive to the more commonly used antibiotics. The drug is of no value in the management of disease due to Gram-negative bacilli, such as *E. coli*, *A. aerogenes*, *Proteus*, and *Pseudomonas*.

Ristocetin is not absorbed from the gastrointestinal tract and requires intravenous or intramuscular injection when used to treat systemic infections.

Thrombophlebitis occurs at the site of intravenous injection of ristocetin. Skin eruptions and fever have followed use of the drug. Rarely, depression of the white blood count with the development of neutropenia may occur. Thrombopenia, with and without bleeding into the skin and mucous membranes, has also been observed. Patients receiving ristocetin should have white blood counts carried out every other day. Smears of the blood should be studied carefully for the presence of an adequate number of neutrophils and thrombocytes; in questionable cases, it is important to determine the total number of platelets.

Nystatin (Mycostatin). Nystatin is poorly absorbed from the gastrointestinal tract. High blood levels follow intravenous injection. This antimycotic agent is employed for local application in the form of ointments, solutions, powders, suppositories, and gels. Topical use in the treatment of *Candida* infections of the skin and vagina has been reported to be successful.

Amphotericin B (Fungazone). This drug is of value in therapy of cryptococcosis (torulosis), histoplasmosis, blastomycosis, coccidioidomycosis, and disseminated moniliasis. It is administered by the intravenous or intramuscular route.

The initial intravenous administration of amphotericin B is usually associated with a febrile response often combined with chills. These reactions tend to diminish with each succeeding infusion and may be limited by prophylactic oral administration of antipyretic or antihistaminic agents. It is best to stop administration of the drug temporarily during a febrile reaction. Headache, nausea, and vomiting may occur early in treatment; when these symptoms appear, the dose should be reduced to a level at which these manifestations do not appear. Increase in nonprotein nitrogen of the blood may occur. The NPN should not be allowed to exceed 40 mg/100 ml. In order to maintain normal levels or to reduce elevated ones to normal, the antibiotic should be temporarily withheld or given on alternate days. Phlebitis may follow infusion of amphotericin. The incidence of this can be reduced by lowering the concentration of drug in the solution to less than 1.0 mg/10 ml and decreasing the rate of flow and the gauge of the needle. Therapy must be stopped immediately if any other toxic manifestations are observed.

Nitrofurantoin (Furadantin). Nitrofurantoin (N-(5-nitro-2-furfurylidene)-1-aminohydantoin) is an antibacterial agent of value primarily in the treatment of some types of urinary tract infection. The drug is bacteriostatic; in high concentrations, it is bactericidal. Nitrofurantoin is most active against *E. coli* (bactericidal), of intermediate effectiveness against *A. aerogenes*, and completely without effect against *Ps. aeruginosa* (*Ps. pyocyaneus*). The activity of the drug against *Proteus* is variable, although many strains are very sensitive. *S. pyogenes* var. *aureus* and enterococci are inhibited by low concentrations.

Nitrofurantoin is administered orally. The estimated degree of antibacterial effect in the urine may at times exceed the apparent in vitro solubility curves in the same medium. With highly alkaline urine, as is the case in *Proteus* infection, the inhibitory effect of nitrofurantoin appears to be depressed; for this reason, simultaneous administration of an acidifying agent has been suggested. Development of bacterial resistance to the drug has not been noted.

Infections of the urinary tract which respond most favorably to therapy with nitrofurantoin are the acute and uncomplicated ones. Infections produced by *E. coli* are the most easily eradicated by this agent. Those due to *Ps. aeruginosa* are totally unaffected, and infections caused by *A. aerogenes* occupy an intermediate position. *Ps. aeruginosa* may appear in the urine for the first time during a course of treatment with nitrofurantoin. Although the drug has been said to be most active against *Proteus* infection, the results are variable. Not infrequently, this organism is only temporarily suppressed and reappears after cessation of therapy.

Nitrofurantoin has been recommended for treatment of some cases of systemic infection due to strains of *S. pyogenes* var. *aureus* and Gram-negative bacilli sensitive to this agent. It is particularly apt to produce severe acidosis

which is difficult to correct in patients who have any degree of renal failure. Determination of plasma  $\text{CO}_2$  at least once a day is imperative in all persons who are being given this agent intravenously. If acidosis is detected, treatment should be stopped immediately, the acidosis repaired, and no further administration of nitrofurantoin allowed. It is safest not to expose any patient to this drug who is known to be acidotic.

Sulfamethoxypyridazine (Kynex, Medice). Sulfamethoxypyridazine (3-sulfanilamide-6-methoxypyridazine) is well absorbed from the gastrointestinal tract and is excreted slowly in the urine. It penetrates the spinal fluid well and has antibacterial activity about equal to that of sulfadiazine. Sulfamethoxypyridazine is most useful in instances in which prolonged therapy or prophylaxis are the objectives; chronic treatment of urinary tract infections and the prevention of rheumatic fever recurrence are two of the indications for the use of this agent. Among the untoward effects which have been observed after the use of this sulfonamide compound are nausea, vomiting, fever, skin eruptions, bone marrow depression with granulopenia or thrombopenia or both, and toxic hepatitis. Attention should be paid to quantity of urine output, as pointed out above.

Sulfamethoxypyrimidine (Madribon). Sulfamethoxypyrimidine (2,4-dimethoxy-6-sulfanilamide-1,3-diazine) is another sulfonamide which is rapidly absorbed and slowly excreted. Sulfamethoxypyrimidine diffuses relatively poorly into cerebrospinal fluid.

Although this sulfonamide, like sulfamethoxypyridazine, has been recommended for therapy of acute infections due to sulfonamide-susceptible organisms, these "long-acting" sulfonamides have no advantages over the rapidly absorbed and excreted ones except the convenience associated with the fact that they need to be taken only once daily. This does not appear to be sufficient grounds to recommend them for therapy of acute infections in place of such clinically well-tested agents as sulfadiazine or sulfisoxazole. It would appear that their greatest area of usefulness is in situations where sulfonamide needs to be given for a long period of time as in control of chronic urinary tract infections, for example, or for prophylaxis of streptococcal infections in rheumatic fever subjects. They probably also have a place in prevention of such diseases as bacillary dysentery and meningococcal meningitis.

Sulfaethylthiadiazole (Sul-Span). Sulfaethylthiadiazole is a rapidly absorbed and slowly excreted sulfonamide which functions on the "sustained-release" principle. The clinical applications for sulfaethylthiadiazole are the same as for sulfamethoxypyridazine and sulfamethoxypyrimidine. Among the untoward effects which have been observed after the use of sulfaethylthiadiazole are nausea, vomiting, skin reactions, and urinary frequency; these occurred in 6% of one group of patients receiving this drug. Attention should be constantly focused on the possibility of the other reactions which have been observed when other types of sulfonamide compounds have been employed. (Part II of this article will appear in the News Letter of 23 September 1960)

### Corticosteroids Activate Tuberculosis

The American Trudeau Society warns that corticosteroids administered to treat other diseases can activate latent tuberculosis. When steroids are administered, patients should first be examined for tuberculosis. Administration of isoniazid may then be indicated.

Prevention of such a medical catastrophe is simple:

a. All patients requiring treatment by ACTH or corticosteroids for chronic conditions or for any period of more than 2 weeks should first be examined for evidence of tuberculosis. Such an examination should include a careful history (to rule out symptoms or past treatment for tuberculosis), a physical examination, and a roentgenogram of the chest. In patients under 45 years of age, or in whom there are equivocal chest x-ray findings, a tuberculin test should also be performed, preferably by the intradermal method.

b. During the period in which corticosteroids are prescribed, it is advisable to administer isoniazid to all patients who show evidence of previous tuberculosis and to all young patients who exhibit tuberculin reactions greater than 10 mm in diameter following a dose of 5 tuberculin units (0.0001 mg PPD). A daily dose of 300 mg for adults (8 mg/kg for children) may be given. It is important to follow such patients closely by observing symptoms and by taking roentgenograms during steroid treatment and annually for a year or two afterward to make sure that the protective treatment has been effective. (Statement by American Trudeau Society, Medical Section, National Tuberculosis Association)

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### Swimmer's Itch

"Swimmer's Itch" is a pruritic eruption of the skin caused by minute larvae of certain trematode worms of the genus Schistosoma. This itch may appear on the arms, legs, or trunk of persons bathing or wading in water containing the larvae. It is not a communicable disease nor a fatal one. Outbreaks of "itch" have been reported in many places in the United States including several in California; both fresh and salt water have been involved. Although the affliction is primarily a concern in recreational areas, it has also occurred in connection with the occupations of rice-farming and clam-digging.

The disease schistosome dermatitis, sometimes called cercarial dermatitis, is usually benign in nature. It is produced by the larva or cercaria of the schistosome. The larva is a motile, free-swimming, between-hosts stage in the life cycle of the schistosome. One of the hosts—the intermediate host—from which the larva or cercaria has emerged is a snail. The definitive host which the larva is seeking and in which it matures to the

adult fluke (worm) is a vertebrate—usually a bird. In many cases the bird will be a water fowl.

In the definitive host the cercaria enters the circulatory system and grows to the adult fluke. The adult worm lays eggs which eventually find their way into the bird's intestinal canal and are passed with the bird's feces. Reentering water in the bird droppings, the eggs hatch into another larval form called a miracidium. In order to stay alive longer than a few hours, these free-swimming miracidia must contact and enter an aquatic snail, the intermediate host.

In the snail tissue, one miracidium can give rise to reproductive stages from which many cercariae are produced. These cercariae burrow out of the snail and swim away in search of a suitable host in which to complete their life cycle. If they make contact with a warm-blooded animal, they are stimulated to penetrate. Since man is not a definitive host for this species of schistosome, the cercaria while capable of penetrating the skin usually dies near the point of entry. The dermatitis reaction occurs in the vicinity of the dead parasite.

The dermatitis reaction appears to take place in two phases. The first is an itching sensation at the time of penetration—usually subsiding after a few minutes—together with some reddening of the skin at the site of entry. After 10 to 15 hours, a second and more intense itching occurs with the formation of papular eruptions. The pruritis persists for several days. The secondary reaction may not appear until after several exposures.

Many kinds of birds—including those that migrate for long distances—are implicated as definitive hosts. Suitable snails seem to be quite common. Man is an unsuitable or accidental host. Known occurrences in California have been few, but several different habitat types have been represented. Fresh water ponds, lakes, and reservoirs in the lowlands and mountains were included. Also involved were quiet marine bays and rock pools on the coast. (G. Grodhaus, Review of the Natural History of Schistosome Dermatitis in California: Vector Views, April 1960)

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### Tuberculin Testing

The value of tuberculin testing for casefinding in children and contacts has been stressed in recent years by Myers, Heaf, and Hsu. This 15-year review shows the value of serial tuberculin testing in an adult group—who are not known contacts and are in apparent good health—in the following ways:

Reactors are declining steadily.

The rate of tuberculin conversions is declining.

About 33 per 1000 were converted during the 15 years.

Men were converted more often than women.

All age groups were converted at about the same rate. Of convertors, about 31 per 1000 progressed to active tuberculosis—approximately equally for men and women. Convertors in age groups up to 39 years yielded the majority of active cases.

The majority of convertors becoming active did so within 4 or 5 months.

Cases of active tuberculosis where the tuberculin test was the first step in diagnosis showed an excellent prognosis.

The rate of staff members with arrested tuberculosis has steadily declined.

(A. L. Rice, Tuberculin Testing in Ontario Mental Hospitals - A 15-Year Review of Staff: *Dis Chest*, 37: 627-631, June 1960)

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### Influenza Death Rates

From figures computed by the Office of Vital Statistics, Department of Health, Education, and Welfare, an interesting comparison may be made between the death rates (per 100,000 inhabitants) of influenza and pneumonia occurring during the first 3 months of 1959 and 1960:

Death rates by age, United States  
January-March 1959\* and 1960

All ages	Influenza and Pneumonia	
	1959	1960
Under 1 year	386.4	335.3
1 - 14 years	8.5	10.2
15 - 24 years	3.1	5.5
25 - 44 years	6.0	13.5
45 - 64 years	27.3	54.4
65 - and over	253.8	457.4
All Ages	40.7	65.6

\*Alaska and Hawaii excluded.

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Control of Communicable Diseases in Man

An official report of the American Public Health Association, Control of Communicable Disease in Man, Ninth Edition revised April 1960, with Navy distribution as NavMed P-5038, may be procured in accordance with BuMed Instruction 5604.1C, 29 April 1960. Also, the publication may be purchased from the American Public Health Association, 1790 Broadway, New York 19, N. Y.

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